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# Uterine Cervical Cancer Screening

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## Abstract

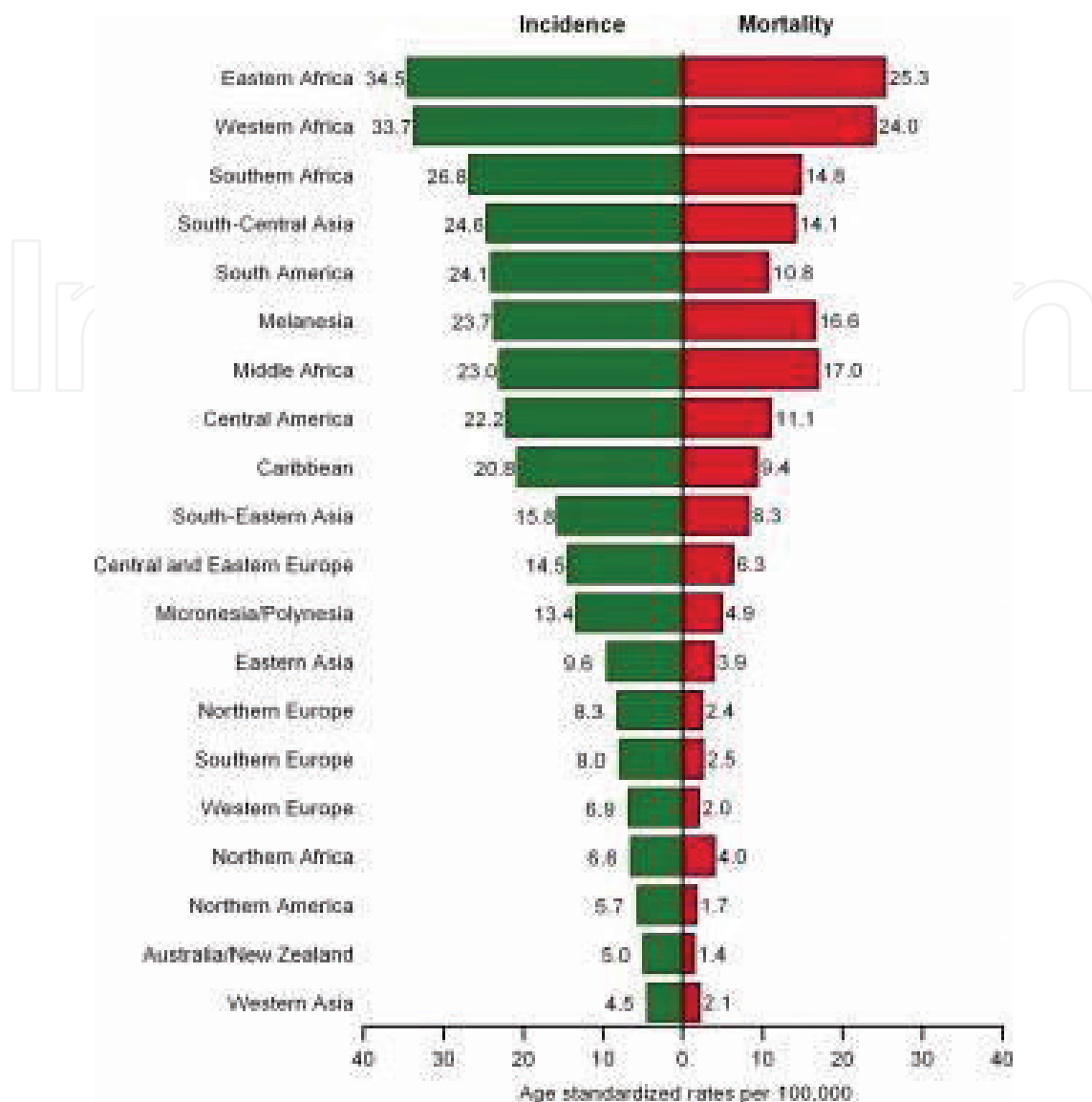
Cervical cancer is the fourth most common cancer and the third cause of death among women worldwide. More than 85% of the cases occur in developing countries. In Latin America, cervical cancer is the most common cause of cancer deaths among women, primarily in young women with devastating social impact. It is mostly the consequence of lack of a health care infrastructure that allows cervical cancer screening suitable for detecting pre-malignant lesions. With the knowledge that human papillomavirus (HPV) infection is the main cause of cervical cancer, two major preventive interventions have emerged: HPV vaccination and screening, which involve the detection and treatment of cervical dysplasia and early-stage cervical cancer. HPV 16 and 18 cause up to 70% of all cervical cancer cases in Latin America and are covered in all available vaccines. Since tests for high-risk HPV types and HPV vaccines are expensive and they have not been included in immunization programs and given free of charge to eligible women in Venezuela and most less developed regions, screening campaigns with cytology and direct visualization of the cervix with VIN continue to be the major interventions that can prevent cervical cancer in these countries; they need to be implemented in a large scale.

**Keywords:** cervical cancer screening, human papillomavirus, HPV vaccine, PAP test, Papanicolaou, cytology, acetic acid, oncogenic HPV

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## 1. Introduction

Cervical cancer is a public health problem in adult women in developing countries of South America, Central and Sub-Saharan Africa, meridional and Sub-oriental Asia [1]. It is the fourth most common cancer and the third cause of death among women worldwide [2]. Nine percent (529,800) of new cancer and 8% (275,100) of all cancer deaths in 2008 were caused by cervical cancer. More than 85% of the cases occur in developing countries. Twenty-seven percent (77,100) of all cervical cancer deaths occurred in India, the second most populous country in the world (**Figure 1**).



**Figure 1.** Age-standardized cervical cancer: Incidence and mortality. Rates by world area. GLOBOCAN 2008.

In 2017, the American Cancer Society (Cancer Statistic Center) estimated that there will be 12,820 new cervical cancer patients and 4210 deaths. The incidence rate for cervical cancer from 2009 through 2017 is 7.6 per 100,000 women; the rate of death from 2010 through 2014 is 2.3 per 100,000 women. The incidence and death rates for cervical cancer in Latin America are still high; for example, in Venezuela, the annual average of new cervical cancer cases from 2010 through 2014 was 4019, with a standardized rate on 2014 of 24.88.

In developed countries, most patients are diagnosed in the early stage of the disease or with pre-malignant lesions susceptible to effective treatment. Nevertheless, with the current migratory movement of women, there is an upturn of advanced stage cervical cancer, especially among women who miss their routine gynecologic evaluation or belong to immigrant’s groups without suitable medical assistance.

In Latin America, cervical cancer occupies the second position after breast cancer and is the most common cause of cancer deaths among women, primarily in young women. For public

health, the principal importance is that cervical cancer mainly affects young women from low income households, with a devastating impact on them and their families with lot of orphans. Despite it being an easily preventable disease, prevention and screening of cervical cancer are not up to the mark in these regions. If prevention and screening programs do not improve, it is estimated that the annual cases will increase with estimation for 2025 of 126,000 new cases [3].

The highest incidence and mortality of cervical cancer in developing countries and other medically unattended areas is mostly the consequence of lack of a health care infrastructure that allows screening suitable for detecting pre-malignant lesions [4]. The most efficient and profitable screening techniques [5] are cytology-based screening (the Pap test) and HPV DNA screening. A clinical trial in one of India's rural areas with low income households found that 1 round of HPV DNA screening was related with a 50% reduction in probability of developing cervical cancer [6].

Screening programs fail because of substandard quality of pap-smear sampling techniques, methodology errors, limited geographical and population coverage with emphasis on high-risk women, and sub-optimal follow-up.

With the knowledge that HPV infection is the main cause of cervical cancer, two major interventions that can prevent cervical cancer have emerged: HPV vaccination and screening, which involves the detection and treatment of cervical dysplasia and early-stage cervical cancer.

All HPV vaccines currently available cover HPV 16 and 18 that cause up to 70% of all cervical cancer cases in Latin America [7]. Cervarix from GlaxoSmithKline is a bivalent vaccine that covers only HPV 16/18; Gardasil from Merck & Co is a quadrivalent vaccine that covers HPV 16/18 and HPV 6/11, which cause genital warts. Both vaccines prevent primary VPH infection, CNI2 and CNI3 related to HPV 16 and HPV 18, when 3 doses are completed. The 9-valent vaccine (Gardasil 9 from Merck & Co.) covers seven HPV types related to cervical cancer, including HPV 16/18 and HPV 6/11 [8, 9].

HPV vaccine is recommended for girls aged 9–26 years of age to prevent cancers of the cervix, vagina, and vulva related with HPV 16 or 18, or genital warts (HPV 6 or HPV 11), and lesions related with other HPV types, cervical adenocarcinoma in situ, vulvar or vaginal intraepithelial neoplasia [10]. In addition, women must be vaccinated before their first sexual activity, prior to exposure to HPV. HPV vaccination is also recommended for women with weakened immune systems (including people with HIV infection), given their higher risk of having HPV infection.

By mid-2016, 65 countries had introduced HPV vaccines, mostly developing countries, but including an increasing number of middle and low-income countries. Unfortunately, HPV vaccines are expensive and they have not been included in immunization programs and given free of charge to eligible women in Venezuela and most less-developed regions. Thus, screening continues to be the major intervention that can prevent cervical cancer in these countries.

## 2. Risk factors

Most of the risk factors for developing cervical cancer are associated with a compromised immune response that allows HPV infection, the etiologic agent of nearly all cases of cervical cancer. These factors include the following.

- Early first sexual intercourse; the risk increases if the first sexual activity is before 21 years of age [11, 12], being approximately 1.5% when first sexual activity is at 18–20 years of age and younger.
- Multiple sexual partners.
- High-risk sexual partner, for example, a partner with multiple sexual partners or with HPV infection.
- Squamous vulvar intraepithelial neoplasia or vaginal neoplasia (highly associated with HPV infection) in the past.
- History of sexually transmitted disease (chlamydia, genital herpes) [13, 14].
- Immunosuppression: VIH-positive women have consistently shown to be at an increased risk for high-grade cervical dysplasia. [14]
- Young age at first full-term pregnancy (less than 20 years of age) and high parity are exogenous cofactors associated with an increased risk of cervical carcinoma; these factors are thought to increase the risk through the maintenance of the transformation zone on the exocervix for a prolonged time, which facilitates exposure to HPV [15].
- Low income/socio-economic status is associated with cervical cancer; incidence and mortality are higher in high-poverty communities [16].
- Oral contraceptives: The data analysis of 24 epidemiologic studies [17] found that the risk of cervical cancer increases with increasing duration of oral contraceptive use (5 years or more of using oral contraceptives vs. non-users); the relative risk was 95% and it decreased after use of oral contraceptives has ceased; the same analysis estimated that 10-year use of oral contraceptives that started at 20–30 years of age increases incidence of cervical cancer in middle-age women
- In current smokers, a doubling in risk of developing cervical cancer has been observed, with a positive correlation with the habit intensity; nicotine and smoke derivatives from tobacco discovered on cervical mucus suggest a possible biologic mechanism through immunosuppression that favor infectious agent such as HPV; tobacco smoking is associated with squamous cervical cancer [18]
- Some daughters of women, especially young women, who took diethylstilbestrol during pregnancy have developed clear cell adenocarcinoma of the cervix and vagina [19, 20]
- High incidence of cervical cancer is observed in Afro-Americans, Latins, and ethnic groups with low incomes and socio-economic conditions with limited access to effective screening and health system [18]

### 3. Genetic factors

There is no established model for a genetic base, although population studies have found increased risk in familiar groups. In the past, it was attributed to ambient environmental

exposure and shared risk factors; however, subsequent data comparing sisters and half-sisters far exceed shared environments.

Research has been done to identify genetic alterations that can make women more susceptible to cervical cancer because of less resistance to HPV infection and persistent infection.

To date, results show a large polymorphism diversity in a wide variety of genes, including those regulating immunity and susceptibility [19–21] and generating a large amount of immune mechanism (cytokines production, angiogenesis, tumor suppression pathways, transcription activation) [22–24].

#### 4. Human papillomavirus

The causal role of HPV in all common and non-common histologic types has been firmly established biologically and epidemiologically and has led to a new carcinogenic model for cervical cancer: HPV acquisition, HPV persistence, progression of pre-malignant lesion to invasive cancer [25, 26]. Human papillomavirus is acquired through sexual contact; most population prevalence reaches its peak few years after the median age of initiation of sexual intercourse.

Most HVP infections are transient, lasting no more than 1 or 2 years [27]. Persistent HPV infection for 1–2 years, especially by HPV 16 predicts development of CIN 3 (cervical intraepithelial neoplasia) or malignant changes. The probability of untreated CIN 3 transforming into an invasive cancer is 30%, although 1% of treated CIN 3 transforms into an invasive cancer [28].

There are more than 100 HPV types; high-risk types 16, 18, 31, 35, and 39 are linked to malignant transformation [29]. Type 18 infection progresses with bad prognosis based on recorded survival rates.

High-risk HPV infection may generate some of the following cell biologic alterations leading to malignant transformation. Two of the eight proteins encoded by the HPV genome, E6 and E7, accounts for most carcinogenic effects of high-risk HPV types. They promote carcinogenesis in several ways:

- They interfere with important tumor suppressor pathways; E6 inhibits the p53 tumor suppressor by promoting its proteasomal degradation, while E7 disrupts the retinoblastoma (Rb) pathway [30, 31], or activates oncogenes via EGFR (epidermal growth factor receptor) [32, 33].
- They induce telomerase enzyme activation related with the unlimited potential of neoplastic cells replication [34].
- E6 and E7 abrogate cell cycle checkpoints and induce genomic instability. Both can induce abnormal centrosome numbers and centrosome abnormalities. They also have synergistic effects on centrosome abnormalities and chromosomal instability [35, 36].



Progression of HPV infection to uterine cervical cancer is associated with progressive histologic changes. Cervical intraepithelial neoplasia (CIN) is a histologic change corresponding to dysplasia of cervical squamous epithelium associated with HPV infection and is considered a potential precursor of uterine cervical cancer. They are classified into three grades: CIN grade I, mild dysplasia, or abnormal cell growth confined to the basal 1/3 of the cervical epithelium; CIN grade II, moderate dysplasia confined to the basal 2/3 of the epithelium; and CIN grade 3, severe dysplasia that spans more than 2/3 of the epithelium, and may involve the full thickness.

Historical data demonstrated that the majority (71–90%) of CIN 1 lesions *regress spontaneously* in contrast with persistence and progression rates for CIN 2 and CIN 3, estimated in 57 and 70% respectively [37].

There are mainly four steps implicated in the development of uterine cervical cancer:

1. Oncogenic HPV infection of squamous cells in the transformation zone of the cervix, which is in the union area of the squamous epithelium of the exocervix and the endocervical glandular epithelium.
2. Persistent HPV infection.
3. Progression of persistent HPV epithelial cells infected to a pre-malignant lesion.
4. Development of invasive carcinoma: Tumor cells in the epithelium cross the basement membrane and invade the stroma.

Formal epidemiological evidence of the association between HPV and cervical cancer did not exist until the early 1990s, although molecular characterization of one of the first types of HPV in the 1980s made it possible to develop tests of hybridization to obtain fragments of HPV genes in human tissue. Using hybridization studies based on polymerase chain reaction (PCR), studies have been conducted for the identification of HPV DNA. One of the pioneer studies in Latin America was carried out by the Agency for Research of Cancer, between Colombia and Spain. The results of this study have been considered as the first evidence of the causal association between HPV and cervical cancer. Subsequently, similar studies were carried out in 9 countries (Algeria, Brazil, India, Mali, Morocco, Peru, Paraguay, Thailand, and Philippines) between 1985 and 1988 to evaluate the role of the virus of HPV in the etiology of CIN 3. The DNA was obtained by cytology and was evaluated by Virapap and PCR. In Spain, HPV prevalence based on PCR was detected in 63.2% of the cases and for controls was observed in 47%. In Colombia, HPV DNA was detected in 63.2% of the cases and in 10.5% of the controls. VPH 16 was the most predominant type of virus and showed stronger association with the development of CIN 3. HPV of unknown origin was common in positive cases (18.3% in Spain and 38.0% in Colombia [28]. In 2006, a study was carried out at the gynecologic department of the Padre Machado Hospital, in Venezuela; it included 58 patients with uterine cervical cancer. Typification of human papillomavirus by PCR for types 6, 11, 16, 18, 31, 33, and 35 were performed; other variables such as age, stage, and histological type were also analyzed. The purpose of this study was typification of HPV in women with invasive

uterine cervical cancer in Venezuela, identification of the country's most frequent HPV type, and comparison with worldwide incidence of VPH. HPV DNA sequences were associated in 52.3% of the patients, VPH 16 in 24.52%, and HPV 18 in 7.4% of their population. These results suggest the imperative need of large-scale epidemiological studies as these results do not reflect the results reported in other countries [38].

## 5. Uterine cervical cancer screening

Screening of uterine cervix decreases the incidence and mortality of cervical cancer. Cervical cancer has two main histological types: squamous and adenocarcinoma. Screening can detect precursors and early stage for both types, and treatment of precursors can prevent the development of invasive cancer. Currently, in addition to screening, test for high-risk human papillomavirus types, which form the foundation of uterine cervical cancer pathogenesis, has been included. In view of the high incidence and mortality of cervical cancer, its significance as a global public health problem, and the difficulties involved in establishing effective screening in different regions of the world, the American Society of Oncology (ASCO), in the year 2013 [39], released a world guide for cervical screening and follow-up of positive cases, as well as guidelines for treatment for pre-malignant lesions. The main recommendation was screening for cervical pre-cancers for all women in appropriate age groups and establishing consistent minimum standards for screening considering and based on resource levels and health systems infrastructure.

Based on the results of a large clinical trial in India that demonstrated that cervical cancer screening with acetic acid (vinegar) could prevent thousands of deaths each year in developing countries [39], initial visual inspection with acetic acid (vinegar) was incorporated in the global screening guideline.

Cancer of the cervix is a highly preventable disease; low-income countries lack large-scale screening and vaccination programs against HPV. As a result, more than 85% of the world's cervical cancer diagnoses and deaths occur in less developed regions. Access to programs of detection and treatment of cervical cancer varies not only between countries but also within them. Standards were established in four different areas of health: basic, enhanced, and maximum limited. These levels correspond not only to the financial resources of a country or region, but also the strengths of the health care including personnel, infrastructure, and access to health systems.

ASCO's guideline builds upon WHO's recommendations by providing a minimum set of standards across all countries based on their existing resources, and by accounting for the 2013 VIA study and other recent data. HPV DNA testing is recommended in all resource settings and VIA may be used while HPV testing becomes available. If VIA, as a primary screening, gives abnormal results, women should receive treatment. After a positive HPV DNA testing result, VIA is recommended for follow-up in basic and limited settings. For other settings, HPV genotyping and/or cytology may be used for triage. Women with abnormal triage results should receive immediate treatment in basic and limited settings, or colposcopy in



all other settings. Screening is recommended for women of ages 25–65 years every 5 years and for ages 30–65 years, and if two consecutive tests are negative at 5-year intervals, then every 10 years. In the context of limited setting, screening is recommended for ages 30–49 years, every 10 years and for basic settings, for ages 30–49 years, one or more screens in a lifetime. When a precursor lesion is diagnosed, the recommended treatment includes LEEP, or ablative treatments (cryotherapy, cold coagulation) with a 12-month post-treatment follow-up for all settings. For women who are HIV positive, those who had recently given birth, and those who have undergone a hysterectomy, separate screening recommendations have been provided.

Screening methods include Papanicolaou (PAP) test (cytology) and tests for high-risk human papillomavirus types. Cervical cancer screening detects precancerous lesions in the early stages and their treatment decreases uterine cervical cancer incidence and mortality. In the United States, PAP was adopted in 1950 and in the mid-1980s [40], the incidence of cervical cancer had decreased to 70% [41]. The benefit of screening is that it decreases mortality and the incidence of cancer of the cervix, but information provided by the PAP must be evaluated since infection can be transient and dysplasia can regress spontaneously, especially in young women [42]. Major adverse outcomes of screening are derived for further consequence to methods used for treatment of injuries. The effects on the reproductive system include stenosis, loss of pregnancy in the second trimester, premature births, and rupture of the membrane [43].

Most episodes of HPV infection and many cases of CIN 1 and CIN2 are transient and fail to develop into CIN 3 or cancer. Potential problems associated with positive screening tests are stigmatization of a sexually transmitted disease and inconvenience associated with additional diagnostic and treatment procedures [44]. Getting a positive test at any time of life may contribute to the perception that one is at an increased risk of cancer and a desire for more tests with the consequent possibility of another positive test, the monetary costs involving the control procedures after a positive result, and the higher cost, from the health perspective, of developing cancer [45]. Although any false-positive test has the potential to induce anxiety, quality of life test is usually not included in screening trials. As a result, the number of colposcopies related to CIN 3 and cancer has been regulated. Cervical cancer is rare in young women and adolescents and may not be prevented by cytological screening. The incidence has not changed in developed countries, but in low-income countries, it presents in earlier ages [46].

Screening in adolescents leads to an unnecessary evaluation and treatment of lesions with high potential of spontaneous regression with reproductive long-term problems. Cancer prevention programs in adolescent should focus on massive vaccination for HPV [47].

Among the 21 to 29 year-olds, screening is recommended with PAP every 3 years. For women aged 21 to 29, with two or more consecutive negative cytologic findings [48, 49], there is no evidence that supports a greater interval for detection (3 or more years). For women less than 30 years of age, HPV screening is not recommended, given high chance of transient HPV infections. Positive predictive value of these tests limits the usefulness of them as screening methods. Randomized studies have shown that HPV testing for women less than 30 years of age [48–50] results in high detection of transient infections by HPV and the women undergo unnecessary colposcopies [51].

For women older than 30 years, PAP is recommended every 3 years with co-tests (PAP and HPV) every 5 years if both initial tests were negative. For women older than 30 years, HPV infection has a greater chance of being persistent; it also has uncertain clinical significance. Any other determination of HPV test increases the probability of positive results, with largest number of colposcopies with uncertain results [52].

In women older than 65 years, tests are not recommended if they meet the following criteria:

- No risk factors: No history of abnormal test; not a habitual smoker, or currently smoking; no disease related to HPV; not new couples; not immunocompromised; no exposure to diethylstilbestrol in utero
- Optimal screening: Two consecutive negative tests, co-tests, or three PAP tests in the last 20 years, latest during five previous years [53, 54]
- No history of high grade dysplasia or more

There are some clinical conditions where increased risk of developing CIN and cervical cancer are observed, as in human immunodeficiency virus (HIV)-infected women. This conclusion is based on several trials including the study of Wright et al. [55] where the definition of cervical intraepithelial neoplasia (CIN) prevalence, validity of PAP tests, and the association of risk factors in women infected with HPV virus, demonstrated that these patients are more likely to have a persistent infection with the virus, increased rate of high grade cervical dysplasia, and higher risk of developing cervical cancer.

Immunosuppressed women: Patients with immunosuppressive therapy (organ /bone marrow transplants, prolonged treatment with steroids, systemic disease), infected with HIV present greater persistence of infection with minor ability to regress spontaneously and therefore, they have higher rates of cervical dysplasia and cancer. Information about immunosuppressed women are based on the results of screening women with systemic lupus erythematosus (SLE). High grade dysplasia and subtype of high-risk HPV persistence rates are significantly higher in women with SLE who receive immunosuppressive therapy, than immunosuppressed patients treated for other conditions, or patients with minor SLE receiving treatment [56, 57].

At present, for this group of patients, who are immunocompromised or HIV-infected, it is recommended to start screening at age 21, or PAP and HPV tests should be done at the age when participating in the first sexual relationship.

Women with total hysterectomy, no history of CIN or cervical cancer, operated for benign pathologies have a very low risk of developing cervical cancer and need not undergo screening for cancer of the cervix [58, 59]. Women with sub-total hysterectomy probably share the same risks as patients with preserved cervix and must follow the general guidelines. For those women with hysterectomy and a history of CIN 2/3 or adenocarcinoma in situ, if the diagnosis was made prior to surgery or hysterectomy, the ACOG recommends screening at least 20 years after treatment [60]. The most recent summary of recommendations [61] includes the following:

- Start screening no sooner than age 21, regardless of the age of onset of sexual activity or other risk factors. Between 21 and 29 years of age, PAP smear must be done every 3 years. Between 30 and 65 years, co-testing (cytology more than an HPV test) every 5 years is preferable; if not possible, single cytology every 3 years is acceptable. After the age of 65 years, screening can be discontinued if previous screening has been done and found negative and not CIN 2 (+) during the previous 20 years.
- Screening can be discontinued if there is total hysterectomy (with removal of cervix) and a history of CIN 2 (+).

These suggestions are valid for developed countries that allow the implementation of adequate screening campaigns with all the resources available. However, for developing countries with limited resources, cytology and direct visualization of the cervix with VIN are valid methods.

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